UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/180,653	11/04/98	HANG N	008439-016

021839 HM11/0203
BURNS DOANE SWECKER & MATHIS
P O BOX 1404
ALEXANDRIA VA 22313-1404

EXAMINER	
MOORE,W	
ART UNIT	**PAPER NUMBER**
1652	6

DATE MAILED: 02/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/185,663	Bang et al.
Examiner	**Group Art Unit**
William W. Moore	1652

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-92* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *1-82 and 84-92* is/are allowed.

☒ Claim(s) *83* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Surrender of Original Patent, Duty of Disclosure, & Correction of Patent

1. Applicants are reminded that the original patent must be surrendered or an affidavit submitted averring its irretrievable loss or misplacement prior to allowance of the instant application, and are also reminded that corrections to U.S. Patent No. 4,775,624 made in the Certificate of Correction issued January 8, 1991 must be entered in the patent specification filed herein. See MPEP §§1411.01 & 1416. Applicants are also reminded of the continuing obligation under 37 CFR 1.56 to timely appraise the Office of any litigation information, or other prior or concurrent proceeding, involving Patent No. 4,775,624, material to patentability of the claims under consideration in this reissue application. This obligation rests with each individual associated with filing and prosecution of this application for reissue. See MPEP §§1404, 1442.01 & 1442.04.

The Preliminary Amendment & Publications Made of Record

2. Preliminary Amendment A, Paper No. 3 filed February 4, 1999, was entered as the printed copy of the Sequence Listing. The diskette accompanying Amendment A provides a computer readable form [CRF] of the sequence listing including the nucleotide sequence of a human Protein C-encoding cDNA at columns 4-5 of the specification and in claim 1, and the light chain amino acid sequence described by claim 81. This CRF could not be entered in the PTO database because, as indicated in the "Raw Sequence Listing Error Report" attached hereto, it lacks mandatory identifiers for the information fields 110 and 120, respectively, the "Applicant" and the "Title of the Invention". Publications made of record in the prosecution of the parent application and reconsidered in examining claims 83-92 submitted herein are made of record on the accompanying form PTO-892.

Sequence Rules Compliance is not Mandatory

3. Compliance with 37 CFR §1.821 is **not** required in response to this Office action because the instant application is, in effect, a continuation of an application filed before the

inception of the Sequence Rules. **Full** compliance with the Sequence Rules is suggested, rather than partial compliance, if Applicants desire the USPTO nucleotide and amino acid sequence files to provide the public with a computer-readable, thus computer-searchable, Sequence Listing. A searchable sequence listing would better apprise the public of the claimed subject matter when a patent issues on this reissue application. While Applicants may submit a substitute CRF including the information needed for mandatory identifiers of fields 110 and 120, both an amended CRF diskette and an amended printed copy of the Sequence Listing should further include **all** sequences of ten or more nucleotides, and **all** sequences of four or more amino acids, disclosed in the specification and claims, each with a sequence designation, to bring the application into compliance with 37 CFR §1.821(a). Triplet codons should be separated by spaces in setting forth coding regions of nucleotide sequences in the CRF and printed forms of the sequence listing. 37 CFR §1.822(c)(3). An amended CRF may be submitted in response to this communication that also provides the preproprotein C amino acid sequence present at columns 6-7 of the patent and the Protein C zymogen amino acid sequence presented in new claim 83, or in a claim 83 that is amended in response to this communication. This is because no issue of new matter arises where a nucleotide sequence or an amino acid sequence is already present in the patent specification and described by the claims.

It is noted that 37 CFR §1.821(b), (c) and (d) require that the specification, the initial patent claims, and the reissue claims be amended to state appropriate sequence designations in the format "SEQ ID NO:n" at each occurrence of a nucleotide sequence or an amino acid sequence. A corrected and/or amended CRF diskette and corrected and/or amended paper copy of the Sequence Listing may be submitted at any time during the prosecution of the instant application to bring it into **full** compliance with the Sequence Rules and should be accompanied by a statement of identity of printed and computer readable forms as set forth in 37 CFR §1.821(f).

Claims 83-92 Present No New Matter & Describe the Same General Invention

4. Claims 83-92 filed in this reissue application present no new matter. Each claim defines a scope intermediate between an independent claim of the patent from which it ultimately depends and one or more patented claims that also depend from the same independent claim of the patent. Each of claims 83-92 could have been presented and prosecuted in application Serial No. 06/699,967 pursuant to the restriction requirement therein and each states a scope within the scope of the general invention described by an independent claim from which each depends. This is because each of the independent claims of the patent permits preparation of a DNA existing within a human Protein C-encoding DNA of claims 1 or 68, or of clause (iii) of claim 69, the insertion of such a DNA in a plasmid of claim 2, such as those of claims 91 and 92, and the practice of a method of claim 12 for recombinant production of at least the zymogen form of human Protein C in eukaryotic cells such as those of claims 84-90, i.e., art-recognized insect and mammalian cell lines including the -carboxylation-competent CHO cell line. As noted in the request for reissue, failure to present claims more particularly describing intermediate subject matters, e.g., the human Protein C zymogen contemplated in claim 1 and clause (iii) of claim 69 where N=0 and M=0, might be considered an error in overlooking such available, patentable, embodiments.

Claims 1- 82 Raise No Issues under 35 U.S.C. §112, First Paragraph

5. Claims 1-82 allowed in application serial No.06/699,697, of which this is a reissue application, present no issues of enablement or of adequate written description. Despite the generic phrase, "polypeptide with human protein C activity", at line 3 of claim 1, the scope of claims 1 and 68, taken as a whole, is very limited. None of claims 1, 68, 81 or 82 describe DNA compounds having a nucleotide sequence that can encode an amino acid sequence that diverges from that present in the heavy chain, the light chain, or the intervening activation peptide, of a native human Protein C translation product. Indeed,

claims 1, 68 and 82 permit no divergence from the DNA sequence, set forth in claim 1, of the cDNA that Applicants found. Both this coding DNA sequence and its complement can be readily prepared and inserted in a generic plasmid of claim 2. The specification amply describes construction of plasmids of claims 3-11, 76 and 77 and preparation of host cells required for the methods of claims 13-55 and 70-75, thus amply demonstrating enablement of the generic methods of claims 12, 69, and 80, which require host cells described by claims 56-67, 78 and 79. The prior art considered by the consecutive Examiners who prepared the record that informed the decision in *In re Bell*, 26 USPQ2d 1259 (Fed. Cir. 1993), shows that those of ordinary skill in the relevant arts of molecular biology and genetics knew, as early as 1984, how to design and prepare any and all conceivable nucleotide sequences that encode a given amino acid sequence. Thus claim 81 describing DNA compounds having generic, isocoding, nucleotide sequences specifying the amino acid sequence of the light chain of a human Protein C is enabled because the design and the preparation of such isocoding DNAs was routine as of the February 8, 1985, filing date of application serial No. 06/699,697. Computer programs available at that time were used to design synthetic, isocoding, nucleotide sequences for a given amino acid sequence in order that the nucleotide sequence correspond to the codon utilization frequency, **aka** codon preference, of any host cell in which the artisan desired to have the encoded polypeptide expression recombinantly.

Claims 83-92 Raise No Issues under 35 U.S.C. §112, First Paragraph

6. Like the originally-prosecuted claims 1-82, claims 83-92 submitted herein present no issues of enablement, or adequate written description, under the first paragraph of 35 U.S.C. §112. Claim 81 has no functional limitation and none is inferred for claim 83 dependent therefrom. Because embodiments which are not particularly described in the patent specification and not expressly enabled thereby are trivial embodiments, claim 83 is not rejected under the first paragraph of 35 U.S.C. §112. Trivial embodiments are those

wherein, e.g., a non-naturally occurring linker peptide covalently joins the light chain carboxyl-terminus to the heavy chain amino-terminus. While the patent specification and state of the art might not suggest utilities for trivial embodiments of claim 83, the primary embodiments have utility because a nucleic acid of the claim may be an isocoding DNA sequence encoding the zymogen form of human Protein C or separately encoding at least functioning light chain and heavy chains of human Protein C. The patent specification describes and enables sufficient embodiments for the useful and predictable practice of the subject matter of claim 83 because many nucleic acid sequences can be prepared according to the teachings of the specification to encode polypeptides having amino acid sequences, each of which can be predicted to comprise at least subsets of the native zymogen amino acid sequence. Such polypeptides may be denatured in solution after recombinant expression, then renatured and reduced to form disulfide bonds and generate activated Protein C without undue experimentation given the state of the art when the patent application was filed.

Claim 12 embraces generic methods of producing polypeptides comprising at least the zymogen form of a human Protein C in a host cell and the method claims 84-91 depending therefrom describe subgenera of such methods. Claim 85 is enabled because Protein C in its zymogen form can be separated from other components in the host cells wherein it is produced and either secreted by the cells or recovered after lysis of non-secreting host cells by an immunoaffinity separation process such as that described at columns 54-55 of the specification. Claims 86 and 87 are enabled for the production of an activated human Protein C because the human Protein C zymogen can be activated according to the disclosure at columns 55-57 of the specification. Like claim 80 of the patent, claims 88-90 submitted with this application are enabled by, e.g., Examples 3, 5 and 14 at columns 27-32 and 53-55 of the patent as well as by the state of the art, and level of skill in the art, of molecular biology at the time each of claims 83-92 could have

been presented and prosecuted in application Serial No. 06/699,967 pursuant to the resolution of the restriction requirement stated therein. This is because the state of the art at that time supported the use of alternative mammalian vectors and host cells for the recombinant production of, *inter alia*, 1) the precursor form of human Protein C which is herein referred to as the prepro-form, 2) a pro-form of human Protein C, and 3) the human Protein C zymogen. Plasmid claims 91 and 92 find embodiments in narrower disclosures in the specification and represent sub-genera within the broad genus of claim 2 of the issued patent. Individual species of claims 91 and 92 are represented by, respectively, claims 10 and 6 of the issued patent.

Claims 1-92 Raise No Issues under 35 U.S.C. §112, Second Paragraph

7. Claims 1-82 of the patent and claims 83-92 submitted in this reissue proceeding satisfy the second paragraph of 35 U.S.C. §112 by definitely describing their intended subject matters. The scope of the generic method and plasmid claims 2, 12, 13, 69, and 80 of the patent, and of claims 84-92 submitted herein, can be understood by the artisan to reach multiple embodiments that permit the insertion of the human Protein C-encoding DNAs of claims 1 and 68, and of clause (iii) of claim 69, in a variety of plasmids in a context for expression suitable for producing at least the zymogen form of human Protein C in eukaryotic cells, such as insect cell lines and mammalian cell lines known in the art, including the -carboxylation-competent CHO cell line. The artisan can readily appreciate the intermediate scope defined by plasmid and method claims 84-92 because the patent specification provides many specific examples within the scope of the patented and recently submitted claims and suggests the extent of the scope of claims 2, 12, 13 and 69 of the patent. While claim 83 can be construed to describe several kinds of polypeptide structurally-related to human Protein C, the artisan and the public can understand that it reaches, in its most complex form, a human Protein C zymogen covalently linked at its amino terminus either, i) consecutively to the native propeptide and native signal peptide,

or, ii) to the native propeptide alone, or, iii) to a native propeptide and a heterogeneous signal peptide, or, iv) to a methionine for direct expression. The public and the artisan can also understand that, in its least complex form, claim 83 reaches a DNA sequence having regions that separately encode both the native light chain and the native heavy chain of human Protein C. The public and the artisan can also understand that several polypeptides of intermediate complexity fall within the scope of the claim which comprise both the native light and native heavy chains covalently linked by a spacer peptide that differs from the native 14-amino acid region at positions 156-169 of the zymogen. Where the metes, the bounds, and even the variety of the subject matter embraced by a claim can be comprehended, that claim cannot be considered indefinite

Claims 1-92 Are Allowable over the Prior Art of Record

8. Claims 1-82 and the newly-submitted claims 83-92 are allowable over the prior art considered in the parent application, made of record and reconsidered herein. Each claim of the patent, and each of claims 83-92, requires that a constructed DNA compound, and any plasmid or host cell comprising the DNA compound, either have the specific nucleotide sequence of the region of the cDNA that Applicants discovered which encodes the light chain of a human Protein C or have a generic amino acid sequence encoding the amino acid sequence of the light chain specified by the cDNA found by Applicants. Even though claim 83 does not exclude a DNA sequence capable of directing the expression of a human Protein C heavy chain independent from expression of a human Protein C light chain, indeed does not require that a region encoding the light chain be in any context for expression, the DNA sequence of the claim must somewhere comprise a DNA sequence region encoding the light chain. In response to a prior art rejection in the prosecution of application Serial No. 06/699,967, Applicants canceled the claims 101 and 102 they had presented at pages 3 and 4 of Amendment A, Paper No. 5 filed March 23, 1987, in Paper No. 9. Claims 101 and 102 were considered at pages 3-5 of Paper No. 6 therein

mailed August 10, 1987, to reach a constructed DNA sequence encoding a single polypeptide comprising the amino acid sequence of the activated Protein C heavy chain, and were rejected as obvious over the August, 1984, identification by Foster et al., of record, of a cDNA isolated from a human liver cDNA library and encoding all but the amino terminal region of the light chain of human Protein C.

The rejection of Applicants' other claims under 35 U.S.C. §103 at that time was withdrawn, however, in view of Applicants' arguments in Paper No 9. Applicants first noted that the Foster et al. cDNA lacked the codons specifying "63 of the amino terminal amino acids of the light chain and all 42 of the amino acids for the pre-pro sequence" of a human Protein C. Applicants then argued that the unpredictability of the art would not have made a cDNA encoding the entire human Protein C, including the entire light chain of activated Protein C, obvious at the time the invention was made, thus claims describing constructed DNA sequences comprising sequences encoding the entire Protein C or the entire light chain of the activated Protein C should be free of the art. The claims of the patent were allowed upon Applicants' amendment of Paper No. 9, a tacit agreement that the prior art did not disclose or suggest a DNA encoding a human Protein C light chain.

The September, 1984, teaching of Long et al. of identifying and sequencing a cDNA from a bovine liver cDNA encoding the entire amino acid sequence of a precursor bovine Protein C is among the prior art cited in the prosecution of application Serial No. 06/699,967. The consecutive, October, 1982, teachings of Stenflo and Fernlund of the determination of amino acid sequences of the light and heavy chains of a bovine protein C were also cited as prior art during the prosecution of application Serial No. 06/699,967. All are now reconsidered in view of two decisions of the Court of Appeals for the Federal Circuit published subsequent to the 1988 publication of U.S. Patent No. 4,774,624 relevant to evaluation of these prior art teachings: *In re Bell*, 26 USPQ2d 1259 (Fed. Cir. 1993), and *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995).

Long et al. teach the complete light and heavy chains and intervening activation peptide as well, p. 5655, as a "leader peptide of at least 39 amino acids" at the amino terminus of the light chain region. Long et al. further teach, Figure 3, that the amino acid sequence of the leader peptide of a bovine Protein C shares structural homology with the amino acid sequences of leader peptides of other human and bovine vitamin K-dependent coagulation factors that, like Protein C, are expressed and secreted by human and bovine livers. Long et al. also teach, pp. 5654-5655, that the only difference between the amino acid sequence deduced from the nucleotide sequence of their bovine Protein C-encoding cDNA and the amino acid sequences of the light and heavy chains of a bovine protein C determined by Stenflo and Fernlund is an inversion of two amino acids at the carboxyl-terminus of the heavy chain, attributed to the procedure used by Stenflo and Fernlund.

Stenflo and Fernlund teach, Fig. 4 at page 12174 and Fig. 3 at page 12183, structural comparisons of the amino acid sequences of the heavy and light chains of bovine protein C and the heavy and light chains of related, vitamin K-dependent, bovine coagulation factors. Stenflo and Fernlund also teach, Fig. 4 at p. 12184, that heavy chain amino acid sequences of the compared coagulation factors share from 35% to 45% identity and further teach, Fig. 5 at p. 12174, that the amino-proximal forty-four amino acids in the amino acid sequences of the compared light chain coagulation factors share from 59% to 67% identity while remaining carboxyl-proximal portions of the light chain amino acid sequences of the compared bovine coagulation factors share from 8% to 50% identity. It would have been obvious to one of ordinary skill in the art at the time the invention was made that a generic, isocoding, DNA sequence specifying the 63 amino acids of the human Protein C zymogen light chain not present in the light chain amino acid sequence deduced from the human liver cDNA found by Long et al. would have to specify 28 invariant amino acids among the 63 and might be expected to specify an additional 14 consensus amino acids.

The first two codon positions among all but one of the invariant amino acids shared by Protein C and other coagulation factors are identical and the remaining codon, for tryptophan, is identical at all three positions. Ten of the fourteen consensus amino acids share nucleotides for the first two codon positions among each that are identical to the first two codon positions of the non-consensus amino acid with which each is aligned. The other four may differ at two codon positions. Thus one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation that the nucleotides at 81 of the 189 codon positions required for the portion of the human Protein C light chain coding region absent from the Foster et al. human cDNA would be correspondent to, and identical to, the nucleotides encoding the first 63 amino acids of the light chain of the bovine Protein C in the bovine cDNA taught by Long et al. Since Foster et al. teach the 276 nucleotides encoding the remaining 92 amino acids, 357 nucleotides out of the 465 nucleotides needed to encode a human light chain amino acid were predictable at the time the invention was made. Both Foster et al. and Long et al. teach methods for identifying Protein C encoding cDNAs present in cDNA libraries generated enzymatically with mRNAs of bovine or human livers.

Claims 1 and 68, and clause (iii) of claim 69, each describes a human Protein C-encoding DNA in terms of a single, unique DNA sequence and claims 2-67, 70-80, 82, and 84-92 all require such unique DNA sequences. The disclosure of Foster et al. cannot be combined under 35 U.S.C. §103 with the teachings of Long et al. and of Stenflo and Fernlund discussed herein to render claims 1-80, 82, and 84-92 obvious in view of the reasoning of the court in *Bell*. Where a myriad of alternate products were possible, the appellate panel in *Bell* looked to the unique nature of a claimed product and found that no method of cloning can be combined with a known amino acid sequence to selectively generate a claimed result, "because a method by which a product might be made is insufficient to render the product obvious." 26 USPQ2d at 1532 (citing *In re Thorpe*,

777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985)). The generic, isocoding, DNA sequences described by claims 81 and 83 cannot be considered obvious in view of the reasoning of the court in *Deuel*, particularly where there is no basis in the prior art teachings for predicting the thirteen unknown amino acids that correspond to the thirteen entirely uncertain codons among the 63 codons absent from the cDNA of Foster et al. This is because the court held that combining a teaching of a method for cloning with the teaching of a partial amino acid sequence could not "make obvious a particular result" which is a product, including the human allele Deuel et al. had copied from native cellular mRNA as their "particular claimed cDNA". 34 USPQ2d at 1216. Claims 1-82 are ALLOWED herewith because they are free of the prior art of record and are subject to no rejection herein under the first or second paragraph of 35 U.S.C. §112.

Claims 84-92 Present no Issue of Recapture and are Allowable

9. The subject matters of the newly-submitted claims 84-92 do not correspond to any subject matter rejected over the prior at of record in the prosecution of application Serial No. 06/699,967, thus cannot possibly present any issue of recapture of subject matter deliberately cancelled in that application. Claims 84-92 are ALLOWED herewith because they describe the same general invention embraced by the independent claims from which they depend, which are free of the prior art of record, and because they are subject to no rejection herein under the first or second paragraph of 35 U.S.C. §112.

Claim 83 is Rejected under 35 U.S.C. §251

10. Claim 83 is rejected under 35 U.S.C. §251 as being an improper recapture of claimed subject matter deliberately cancelled in the application for the patent upon which the present reissue was based. As stated in *Ball Corp. v. United States*, 221 USPQ 289, 295 (Fed. Cir. 1984):

> **"The recapture rule bars the patentee from acquiring, through reissue, claims that are of the same or broader scope than those claims that were canceled from the original application."**

While claim 83 includes the subject matter described by the patented claim 81 from which it depends and clearly is within the scope of the patented claim 1, its recitation permits it to also describe a constructed, recombinant DNA sequence comprising regions which **separately** encode the light chain of an activated Protein C and the heavy chain of an activated Protein C. Claim 83 is thus considered to include subject matter described by claims 101 and 102 presented at pages 3 and 4 of Applicants' Amendment A, Paper No. 5 filed March 23, 1987, in the prosecution of application Serial No. 06/699,967. The claims were rejected under 35 U.S.C. §103 over the prior art - the August, 1984, disclosure of Foster et al. - for the reasons set forth at pages 3-5 of Paper No. 6 therein mailed August 10, 1987.

Applicants subsequently requested that claims 101 and 102 be canceled at page 2 of Paper No. 9, Applicants' Amendment B filed February 1, 1988, and the claims of U.S. Patent No. 4,775,624 issuing on the application were allowed in Paper No. 10 mailed April 12, 1998 in view of the cancellations. Even though Applicants explain at page 3 of Paper No. 9 that claims 101 and 102 "are cancelled . . . to speed prosecution of the case to issue", it is clear that they relinquished the subject matter represented by these claims in arguing at page 9 therein that Foster et al. disclose "only a portion of the coding sequence of human protein C" which, in addition to encoding the complete amino acid sequence of the heavy chain of an activated human Protein C, "leav[es] 105 codons, roughly 1/3 of the molecule, for Applicants to provide." Applicants noted, *id.*, that the cDNA of Foster et al. lacked the codons which specify "63 of the amino terminal amino acids of the light chain and all 42 of the amino acids for the pre-pro sequence" and further noted, *id.*, that they "cancelled, without prejudice, Claims . . . 102 and 103 which partly relate to the Foster et al. incomplete sequence", permitting allowance of the remaining claims drawn to constructed DNAs comprising sequences that encode the entire Protein C or the entire light chain of the activated Protein C. A DNA of claim 83 can comprise a further region

which is an improper recapture of subject matter previously canceled and relinquished in the prosecution of the application issuing as the patent, even though the claim requires that a constructed DNA comprise a coding region specifying the light chain of human Protein C, because the further region can separately encode the heavy chain amino acid sequence of the activated human Protein C as disclosed by Foster et al. in a context for independent expression.

It might be argued that the limitation, "comprises the coding sequence for the active light chain of human Protein C . . . having the amino acid sequence . . .", of patented claim 81 is retained in claim 83, thus prevents claim 83 from recapturing the previously relinquished subject matter. But no functional limitation in claim 81 requires that a "constructed, recombinant DNA sequence" encode a single polypeptide, or that it encode any particular polypeptide capable of exhibiting any activity of human Protein C. Thus the recitation of claim 81, extended to claim 83 dependent thereon, cannot exclude separate coding regions - separate reading frames flanked by separate translation initiation codons and translation termination codons - that independently specify separate products, one of which is the heavy chain of human Protein C. Claim 83 reaches both the subject matter which Applicants argued to be free of the prior art, a DNA encoding the entire amino acid sequence of the active light chain of human Protein C, and, impermissibly, the subject matter which Applicants had relinquished to overcome a prior art rejection, a DNA encoding the complete heavy chain amino acid sequence of human Protein C.

The limitations of claim 83 only associate, but do not covalently join in a single reading frame, DNA sequences encoding the light and heavy chains of human Protein C thus fail to specifically limit the informational complexity of the resulting molecule. The prior art that Applicants cited in canceling claims 101 and 102 discloses information present in an enzymatic copy of a naturally occurring molecule of human cells, a Protein C-encoding messenger RNA. Such mRNAs are biopolymers are recognized in the relevant

art of molecular biology to be informational molecules. This art similarly recognizes that cDNA copies of mRNAs, and any other DNAs that otherwise specify the same amino acid sequences or portions thereof, are informational molecules. Such nucleic acid sequences are considered to be primarily informational molecules in the relevant art because they neither have any activity *per se* nor any useful properties in any system that lacks the biological information-processing components of cells: the RNA transcription enzymes, the translational apparatus of the ribosome and its cofactors, transfer tRNAs which provide amino acids in a state supporting polypeptide biosynthesis, and the charging enzymes which join codon-specific tRNAs to their specific amino acids.

Claim 83 expands the subject matter embraced by claim 81 because it permits the previously-relinquished subject matter to be linked to that of claim 81 in a fashion whereby the additional codons can allow the transcription and translation of a Protein C heavy chain amino acid sequence independently of the amino acid sequence of the light chain. Absent a limitation requiring that a "constructed, recombinant DNA" encode but a single polypeptide, claim 83 must be considered an attempt to recapture the subject matter Applicants had relinquished in the face of the prior art in the prosecution of application Serial No. 06/699,967. Claim 83 may be rewritten to describe a single DNA sequence encoding a single polypeptide by describing a constructed, recombinant DNA encoding the human Protein C zymogen. This is a lesser-included subject matter embraced by claim 1 of the patent, a DNA sequence where M=0 and N=0, and such a rewritten claim 83, depending from claim 1 rather than from claim 81, could not be considered a recapture of subject matter relinquished with the cancellation of claims 101 and 102.

It is noted that any amendment to claim 83 requiring the presence of codons which specify a peptide other than the native fourteen amino acids linking the carboxyl-terminus of the light chain to the amino terminus of the heavy chain in a constructed DNA sequence that encodes a single polypeptide comprising the amino acid sequences of the

activated Protein C light and heavy chains, could raise issues of new matter, enablement, and/or an absence of an adequate written description in the patent specification of the claimed subject matter.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is (703) 308-0583. The examiner can be reached Monday through Friday from 9:00 AM to 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published November 15, 1989 in the Official Gazette, 1096 OG 30. Informal and unofficial communications may be sent to the Art Unit 1652 FAX number, (703) 308-0294. Official filings should be sent to the Technical Center 1600 FAX number which is (703) 308-4556.

12. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. §122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

William W. Moore
January 31, 2000

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600